REMARKS

Applicants respectfully request reconsideration and reexamination of the present application in light of the amendments and the remarks below.

Claims 1-8 are pending in this application. Claims 6 and 8 have been amended. These claim amendments are made to clarify the subject matter therein. Therefore, these amendments are submitted in order to place the claims in condition for allowance, and do not disclaim any subject matter to which the Applicants are entitled.

Election of Species

The Examiner has requested an election of a single species for prosecution (pages 2 and 3 of the Office Action dated October 9, 2003).

In response to the election of species requirement, applicants elect Example 4, (+)-4(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid, found on pages 62-63 of the specification for further prosecution in this application.

Claim Rejections

The Examiner rejected claims 1-4 under 35 U.S.C. §§ 101 and 112 since they are drafted in terms of use (page 3 of the Office Action dated October 9, 2003).

Applicants submitted a preliminary amendment at the time of filing the application (Filing Date: March 22, 2002). A copy of the preliminary amendment as filed has been enclosed for the Examiner's convenience.

Claims 1-4 were amended in the preliminary amendment, and the amended claims no longer recite the term "use" (see pages 16-27 of the Preliminary Amendment submitted March 22, 2002).

The Examiner rejected claim 5 as incomplete as it mentions formula I' but such a formula is not in claim 5 (page 3 of the Office Action dated October 9, 2003). Claim 5 was amended in the preliminary amendment and formula I' was incorporated into the claim (see page 27 of the Preliminary Amendment submitted March 22, 2002).

The Examiner rejected claim 6 under 35 U.S.C. 112 as "at least" is open to the inclusion of unknown (page 3 of the Office Action dated October 9, 2003). Claim 6 has been amended as suggested by the Examiner. Specifically, the claim recites "one or more" (see page 14 of this amendment).

The Examiner rejected claim 7 under 35 U.S.C. 103 as the preparation of a composition by mixing is well known since the time of Alchemists working in Caves (page 3 of the Office Action dated

October 9, 2003). Claim 7 was amended in the preliminary amendment and now recites steps in the process of preparing a pharmaceutical composition (see page 27 of the Preliminary Amendment submitted March 22, 2002).

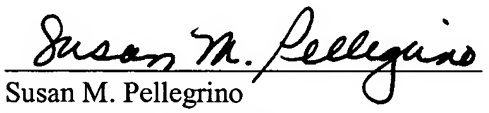
The Examiner stated that claim 8 is not "statutory" as it is claimed in terms of "use," and is recited as a "medicament" (page 3 of the Office Action dated October 9, 2003). Claim 8 has been amended and now recites a method of treatment (see page 15 of this amendment).

CONCLUSION

For the foregoing reasons, Applicants submit that the claims are in condition for allowance and Applicants respectfully request reexamination of the present application, reconsideration and withdrawal of the present rejections, and entry of the amendments. Should there be any further matter requiring consideration, Examiner Ford is invited to contact the undersigned counsel.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 13-3372. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should also be charged to undersigned's deposit account.

Respectfully submitted,



Susan M. Pellegrino
Attorney for Applicants
Reg. No. 48,972

Date: January 2, 2004

Bayer Pharmaceuticals Corporation
400 Morgan Lane
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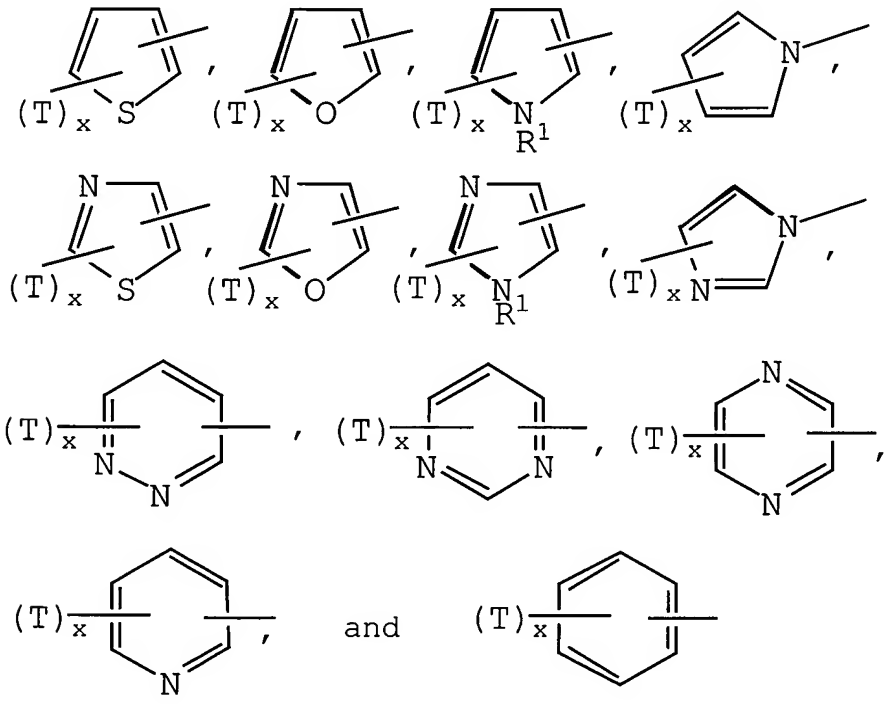
Amended Claims (Attorney Docket No. LeA 33 914)

1. (Previously presented) A method for the treatment or prophylaxis of multiple sclerosis, comprising administering to a mammal an effective amount of a compound of the generalized formula (I):

$$(T)_XA\text{-}B\text{-}D\text{-}E\text{-}CO_2H \qquad (I)$$

wherein

(a) $(T)_XA$ represents a substituted or unsubstituted aromatic or heteroaromatic moiety selected from the group consisting of:



wherein R^1 represents H or alkyl of 1 - 3 carbons; and

each T represents a substituent group, independently selected from the group consisting of:

* the halogens -F, -Cl, -Br, and -I;
* alkyl of 1 - 10 carbons;
* haloalkyl of 1 - 10 carbons;
* haloalkoxy of 1-10 carbons;

* alkenyl of 2 - 10 carbons;
* alkynyl of 2 - 10 carbons;
* $-(CH_2)_pQ$, wherein

  p is 0 or an integer 1 - 4,
* -alkenyl-Q, wherein

  said alkenyl moiety comprises 2 - 4 carbons; and
* -alkynyl-Q, wherein

  said alkynyl moeity comprises 2-7 carbons; and

Q is selected from the group consisting of aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, -CN, -CHO, $-NO_2$, $-CO_2R^2$, $-OCOR^2$, $-SOR^3$, $-SO_2R^3$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-C(O)R^2$, $-N(R^4)_2$, $-N(R^2)COR^2$, $-N(R^2)CO_2R^3$, $-N(R^2)CON(R^4)_2$, $-CHN_4$, $-OR^4$, and $-SR^4$;

wherein

R^2 represents H;

alkyl of 1 - 6 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom; or

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R^3 represents alkyl of 1 - 4 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O or S heteroatom; or

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons; or

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

R^4 represents H;

alkyl of 1 - 12 carbons;

aryl of 6 - 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl in which the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 4 carbons;

heteroaryl-alkyl in which the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

alkenyl of 2 - 12 carbons;

alkynyl of 2 - 12 carbons;

$-(C_qH_{2q}O)_rR^5$ wherein q is 1-3; r is 1 - 3; and R^5 is H provided q is greater than 1, or alkyl of 1 - 4 carbons, or phenyl;

alkylenethio terminated with H, alkyl of 1-4 carbons, or phenyl;

alkyleneamino terminated with H, alkyl of 1-4 carbons, or phenyl]

$-(CH_2)_sX$ wherein s is 1 - 3 and X is halogen;

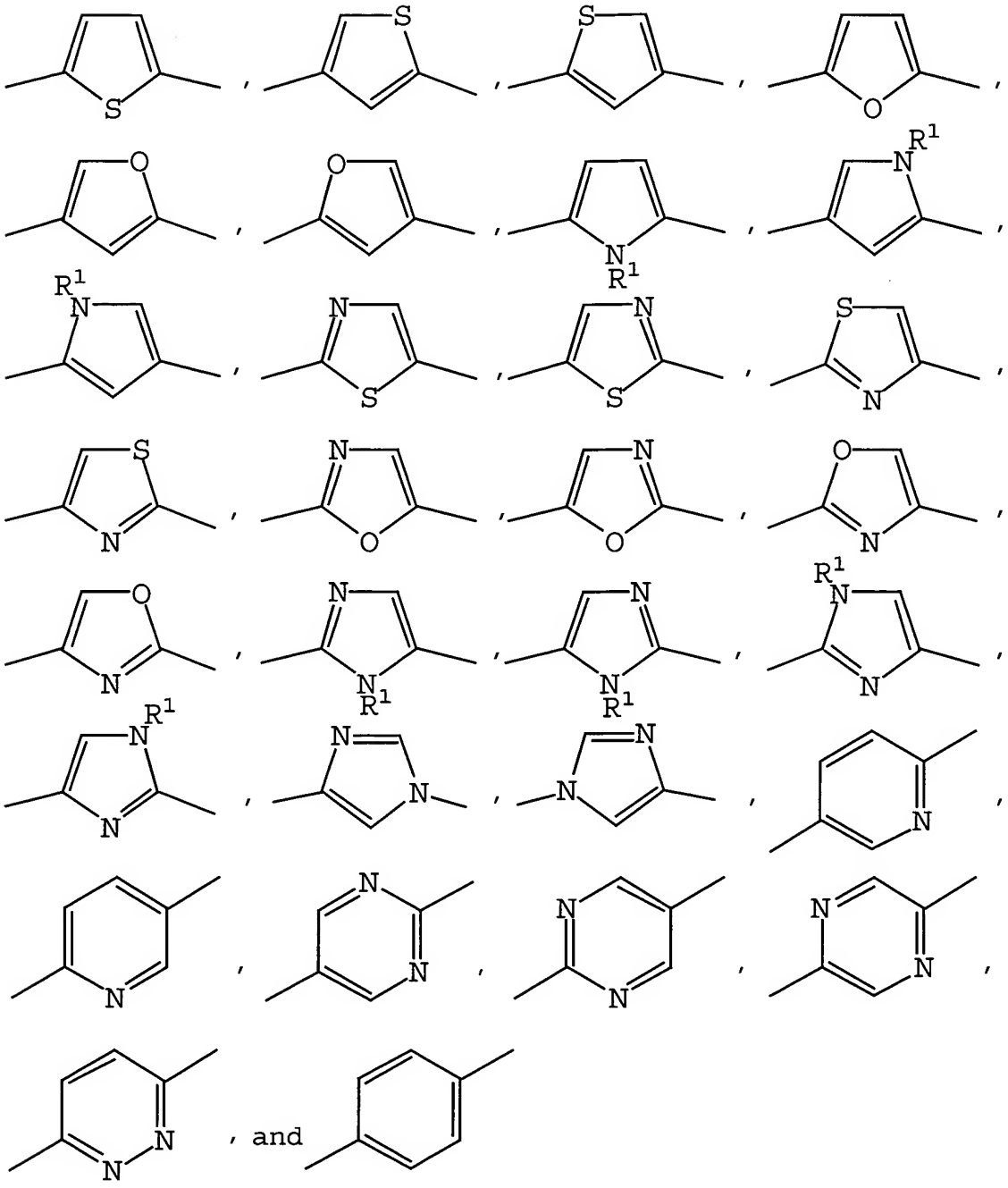
$-C(O)OR^2$; or

$-C(O)R^2$;

and with the provisos that a) when two R^4 groups are situated on a nitrogen, they may be joined by a bond to form a heterocycle, and b) unsaturation in a moiety which is attached to Q or which is part of Q is separated from any N, O, or S of Q by at least one carbon atom, and

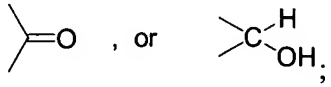
x is 0, 1, or 2;

(b) B represents a bond or an optionally substituted aromatic or heteroaromatic ring containing 0-2 substituents T, which substitutents T may independently have the meaning specified under (a), the B rings being selected from the group consisting of:



wherein R^1 is as defined above; and each R^1 may be the same or different:

(c) D represents



(d) E represents a chain of n carbon atoms bearing m substituents R^6, wherein said R^6 groups are independent substituents, or constitute spiro or nonspiro rings in which a) two groups R^6 are joined, and taken together with the chain atom(s) to which said two R^6 group(s) are attached, and any intervening chain atoms, constitute a 3 - 7 membered ring, or b) one group R^6 is joined to the chain on which said one group R^6 resides, and taken together with the chain atom(s) to which said R^6 group is attached, and any intervening chain atoms, constitutes a 3 - 7 membered ring; and wherein

n is 2 or 3;

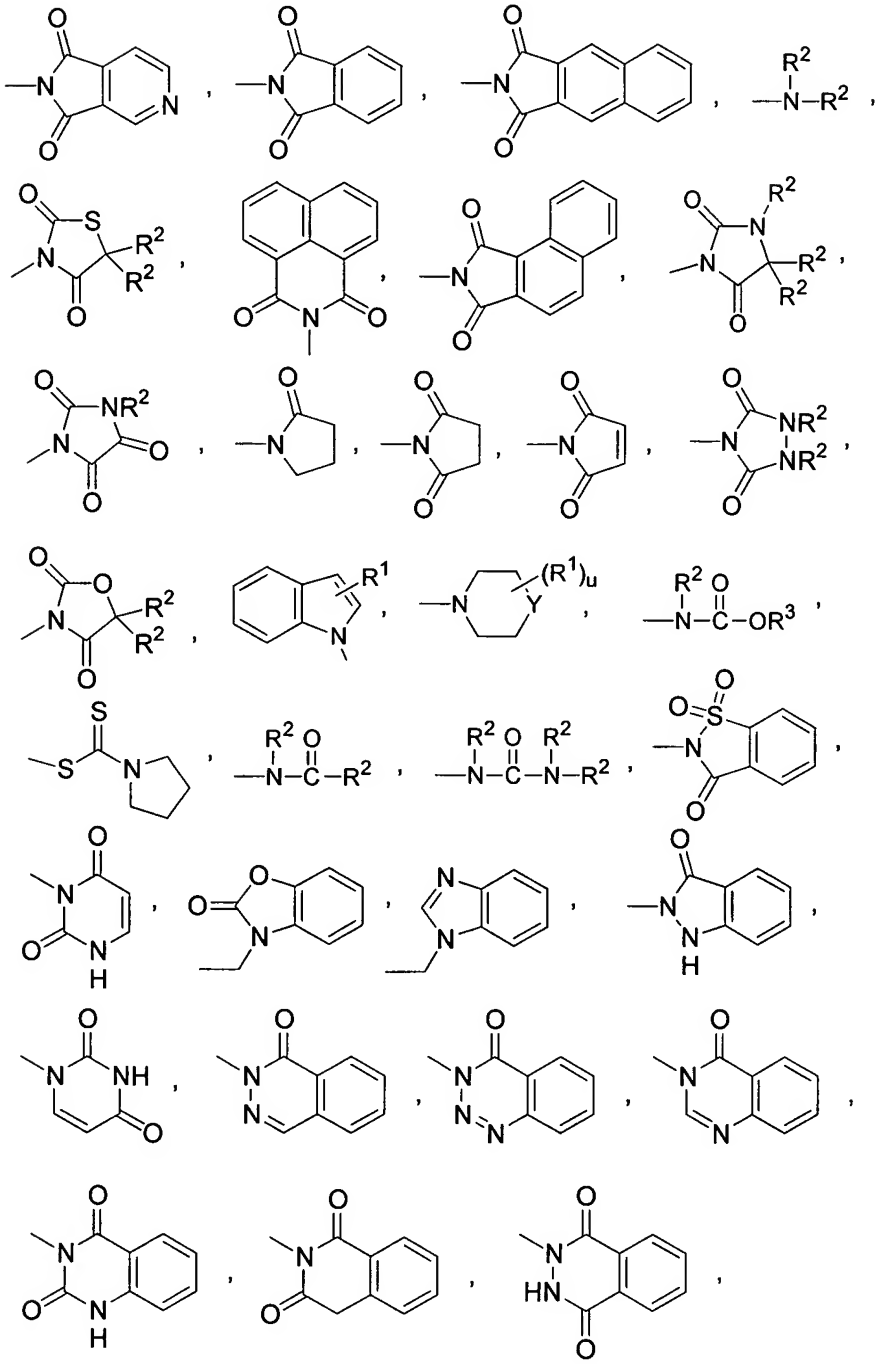
m is an integer of 1 - 3;

each group R^6 is independently selected from the group consisting of:

* fluorine;
* hydroxyl, with the proviso that a single carbon may bear no more than one hydroxyl substituent;
* alkyl of 1 - 10 carbons;
* aryl of 6 - 10 carbons;
* heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;
* arylalkyl wherein the aryl portion contains 6 - 10 carbons and the alkyl portion contains 1 - 8 carbons;
* heteroaryl-alkyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 8 carbons;
* alkenyl of 2 - 10 carbons;
* aryl-alkenyl wherein the aryl portion contains 6 - 10 carbons and the alkenyl portion contains 2 - 5 carbons;
* heteroaryl-alkenyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkenyl portion contains 2 -5 carbons;
* alkynyl of 2 - 10 carbons;
* aryl-alkynyl wherein the aryl portion contains 6 - 10 carbons and the alkynyl portion contains 2 - 5 carbons;
* heteroaryl-alkynyl wherein the heteroaryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkynyl portion contains 2 - 5 carbons;
* $-(CH_2)_tR^7$ wherein

  t is 0 or an integer of 1 - 5; and

R^7 is selected from the group consisting of



and corresponding heteroaryl moieties in which the aryl portion of an aryl-containing R^7 group comprises 4 - 9 carbons and at least one N, O, or S heteroatom;

wherein

Y represents O or S;

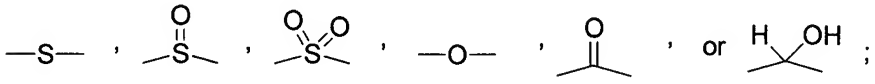
R^1, R^2, and R^3 are as defined above; and each R^1, R^2 or R^3 may be the same or different; and

u is 0, 1, or 2; and

* $-(CH_2)_vZR^8$ wherein

v is 0 or an integer of 1 to 4; and

Z represents



R^8 is selected from the group consisting of:

alkyl of 1 to 12 carbons;

aryl of 6 to 10 carbons;

heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom;

arylalkyl wherein the aryl portion contains 6 to 10 carbons and the alkyl portion contains 1 to 4 carbons;

heteroaryl-alkyl wherein the aryl portion comprises 4 - 9 carbons and at least one N, O, or S heteroatom and the alkyl portion contains 1 - 4 carbons;

$-C(O)R^9$ wherein R^9 represents alkyl of 2 - 6 carbons, aryl of 6 - 10 carbons, heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, or arylalkyl in which the aryl portion contains 6 - 10 carbons or is heteroaryl comprising 4 - 9 carbons and at least one N, O, or S heteroatom, and the alkyl portion contains 1 - 4 carbons;

and with the provisos that

- when R^8 is $-C(O)R^9$, Z is S or O;
- when Z is O, R^8 may also be $-(C_qH_{2q}O)_rR^5$ wherein q, r, and R^5 are as defined above; and

* $-(CH_2)_wSiR^{10}_3$ wherein

w is an integer of 1 to 3; and
R^{10} represents alkyl of 1 to 2 carbons;

and with the proviso that

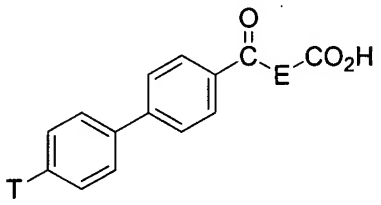
- aryl or heteroaryl portions of any of said T or R^6 groups optionally may bear up to two substituents selected from the group consisting of $-(CH_2)_yC(R^4)(R^3)OH$, $-(CH_2)_yOR^4$, $-(CH_2)_ySR^4$, $-(CH_2)_yS(O)R^4$, $-(CH_2)_yS(O)_2R^4$, $-(CH_2)_ySO_2N(R^4)_2$, $-(CH_2)_yN(R^4)_2$, $-(CH_2)yN(R^4)COR^3$, $-OC(R^4)_2O-$ in which both oxygen atoms are connected to the aryl ring, $-(CH_2)_yCOR^4$, $-(CH_2)_yCON(R^4)_2$, $-(CH_2)_yCO_2R^4$, $-(CH_2)_yOCOR^4$, -halogen, -CHO, $-CF_3$, $-NO_2$, -CN, and R^3 wherein

y is 0 - 4; and

R^3 and R^4 are as defined above, and each R^3 and R^4 may be the same or different; and any two R^4 which are attached to one nitrogen may be joined to form a heterocycle;

or a pharmaceutically acceptable salt or prodrug thereof.

2. (Previously presented) The method according to claim 1 wherein the method comprises administering a compound of the general formula (I')



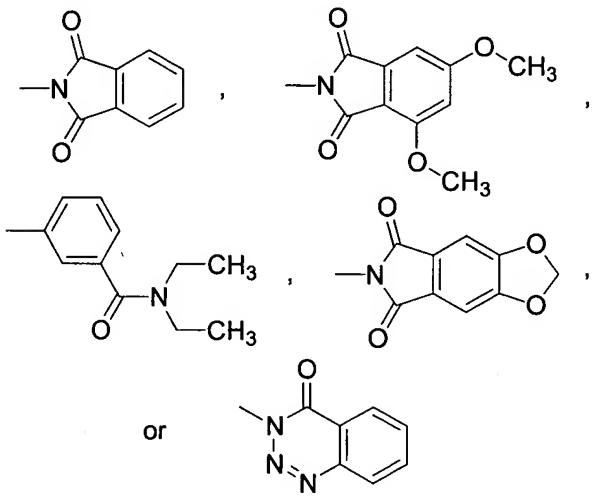
(I')

wherein

T is (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, chloride, bromide, fluoride, acetoxy, hydroxy, cyano, trifluoromethyl or trifluoromethoxy,

CO-E-CO_2H represents a 3-carboxyl-5-(R^7)-pentan-1-on-1-yl- or a [2-carboxyl-3-(R^7)-methyl-cyclopentan-1-yl]-carbonyl-residue, wherein

R^7 represents a group of the formula



or a salt thereof.

3. (Previously presented) The method according to claim 2, characterized in that one emantiomer of a pair of emantiomers at a chiral center adjacent to the carboxylic acid moiety of the group of the formula CO-E-CO_2H in compounds of the general formula (1') more potently inhibits MMP-2 and/or MMP-9.

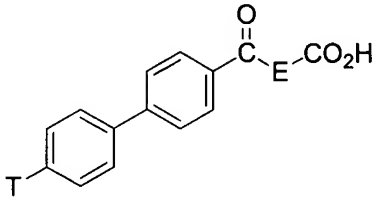
4. (Previously presented) The method according to claim 1, wherein the compound is selected from the group consisting of

(+)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-(4'-ethoxyl[1,1'-biphenyl]-4-yl)-4-oxobutanoic acid,

(+)-4-(4'-chloro[1,1'-biphenyl]-4-yl)-2-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-4-oxobutanoic acid,

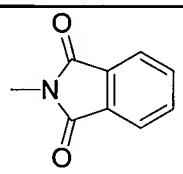
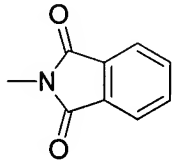
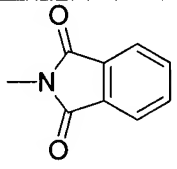
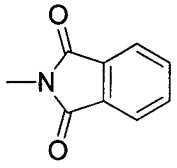
and salts thereof.

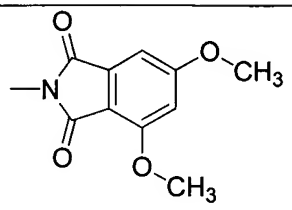
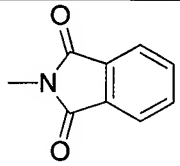
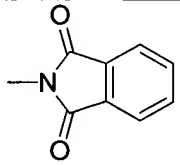
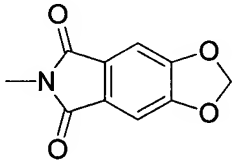
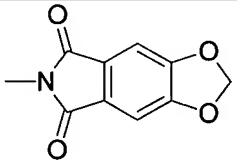
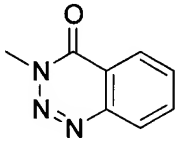
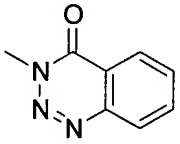
5. (Previously presented) A compound of the general formula (I'),



(I')

wherein CO-E-CO_2H represents a 3-carboxyl-5-R^7-pentan-1-on-1-yl- residue, and wherein T and R^7 have the meaning indicated in the following table:

T	R^7	racemate, (+)- or (-)-enantiomer	
OEt		(+)	;
OEt		(-)	;
OAc		rac	;
OH		rac	;

Cl		rac	;
Br		(+)	;
Br		(-)	;
Cl		(+)	;
Cl		(-)	;
CN		rac	or
OCF_3		rac	.

6. (Currently amended) A pharmaceutical composition which as active constituent contains ~~at least~~ one or more compounds according to claim 5 mixed together with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.

7. (Previously presented) A process for the preparation of a pharmaceutical composition according to claim 6, comprising formulating a compound of claim 5 with at least one pharmaceutically tolerable essentially non-toxic vehicle or excipient.

8. (Currently amended) ~~Compound according to claim 5 for use as a medicament in~~ A method for the treatment of multiple sclerosis, ~~humans or animals~~ comprising administering to a mammal an effective amount of a compound according to claim 5.